

Drug Options

Morphine and the Opioids

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The Role of Opiates and Opioids

The opiates are naturally occurring compounds that originate from the sap of the poppy, *papaver somniferum* and include drugs like morphine and codeine. Opioids are all drugs with morphine-like effects and include semi-synthetic products derived from morphine: drugs like heroin and codeine, along with a number of fully synthetic compounds like pethidine, methadone and fentanyl. These compounds all effect the opioid receptors in the brain and are generally used for the control of strong pain. Other effects include respiratory depression and sedation. It is this combination of sedation and respiratory depression that give this class of drugs a potential for use to end of life.

Morphine and the Opioids

While morphine is the commonest example used in medicine, many other opioid drugs are regularly prescribed as analgesics, including drugs like hydromorphone and oxycodone. The illegal drugs of heroin and carfentanil are opioids. The goal is the easy administration of a single dose of drug to bring about a peaceful and reliable death. Yet all opiates have properties that make them difficult drugs for a person to use to reliably end their life.



Fig 10.1: Greek god Morpheus, god of dreams, with Iris.

The Dual Problems of Sensitivity and Tolerance

The difficulties of using opioids to reliably end life are well can be demonstrated using morphine as an example.

The biggest problem associated with taking opioids is predicting the effect of a particular dose. There is remarkable individual variability in sensitivity to these drugs within the normal population. People who are similar physically (same height, weight, sex etc) can have a vastly different response to the administration of the same dose of a drug.

A small opioid dose may have almost no effect on one person, while that same dose could kill another person. Predicting the effect of the drug on an individual is difficult. When these drugs are used clinically, where accidental death would be disastrous, the rule of thumb has been to ‘start low and go slow’ until the individual’s sensitivity to the drug is established.

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Another difficulty with opioids is the rapid development of tolerance when the drugs are taken for any period of time. Within days, the dose of the drug that initially had a powerful effect on a person's pain can, can become almost ineffective.

To obtain the same pain relief the dose must be increased. If these drugs are taken over a long period, very large doses might be needed to provide adequate pain control. Yet these required doses can become so large that if they had been taken before the person's tolerance had developed, death could well have been the result.

It is this development of tolerance, and its rapid loss once the drugs stop, that often leads to the accidental death of people who self-administer opiates, especially heroin. If there is a break in supply and the acquired tolerance is lost, a sudden resumption may result in an unexpected fatal overdose.

The Opioid Antidote

Another important consideration for a person thinking they might use opioids to end life, is the ready availability of the fast-acting and effective antidote, naloxone. Naloxone competes with the opioids for the receptors in the brain, displacing any of the opioids that are present. Naloxone can rapidly reverse the effects of the drug. People close to death from respiratory failure brought about by a lethal dose of opioid can be rapidly resuscitated when naloxone is administered by injection (or by nasal spray). In the 2016 presidential election, Hillary Clinton announced a policy to make naloxone nasal spray readily available as one part of her policy in dealing with illegal drugs in the US.

<http://www.alternet.org/drugs/hillary-clinton-drugs>

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Anyone using an opioid to bring about a peaceful and reliable death needs to be aware of the existence of the antidote, Naloxone.

Morphine

Morphine is commonly prescribed as a slow release (SR) tablet. MS Contin and Kapanol are marketed forms of morphine. These tablets may be taken once or twice a day. They are designed to slowly release the morphine in order to give 'background' pain control. For the onset of sudden (breakthrough) pain, a fast-release form of the drug such as 'Ordine' (liquid morphine) is often prescribed.

Many very sick people receive these pain drugs in the context of serious illness. Sometimes these very sick people will go to great lengths to stockpile morphine tablets, believing that they can acquire a lethal dose. The problem is, knowing how many morphine tablets to accumulate is like asking the length of a piece of string.

A single dose of SR tablet morphine may cause death, but the result is often unpredictable. The fast-acting liquid morphine may be a more effective form of the drug, but the problems of sensitivity and tolerance remain.

For these reasons it is difficult to recommend morphine as stand-alone, single-dose, oral agent to provide a reliable death.

Morphine does, however, have a role as a supplementary or potentiating agent, (ie. a drug taken to enhance the effectiveness of another drug). While alcohol is the usual potentiating agent, for people who do not drink, liquid morphine can be a good alternative.

Slow Euthanasia - The Doctor's Loophole

Morphine plays a major role in the practice of 'Slow Euthanasia' (or the 'Doctrine of Double Effect' as it is often called). In a country where assisting a suicide is an illegal act, slow euthanasia is the only way a doctor can hasten the death of a patient and escape any legal consequence.

Known commonly as the 'doctor's loophole' slow euthanasia allows a doctor to end a patient's life by slowly increasing the amount of a pain-killing drug. In the eyes of the law it doesn't matter if, in the course of treating a person's pain, the person dies. As long as the stated primary intention is the treatment of the person's pain, the doctor is legally safeguarded. Yet it is the administration of the pain-relieving drug that causes the double effect; it relieves pain but it also causes death.

While slow euthanasia is relatively common, few doctors admit their involvement. Even while administering slow euthanasia, some doctors will argue that they are only treating the patient's pain. Others know exactly what their 'prime intention' is, but wisely decide to keep quiet about it. Others just prefer not to think about it too closely.

It is a pity that this practice is so cloaked in secrecy. Clearly, it would be better if there were open and honest communication between the medical system (represented in the doctor and health care team), the patient and the patient's family. However, in jurisdictions where laws are in place that make it a serious crime to hasten a patient's death, but make it no crime at all to aggressively treat pain, there is little prospect of change.

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How Slow Euthanasia Works in Practice

A doctor practicing slow euthanasia usually gives a narcotic analgesic (morphine), while periodically reviewing the patient's pain. The claim is then made that treatment is inadequate, and the morphine dose needs to be increased.

If this review takes place every 4 - 6 hours, morphine levels will rise. Eventually, lethal levels will be reached and the patient will die. The doctor will defend their actions by saying that they were trying to control the patient's pain. Death, they will argue, was an unplanned consequence of either the patient's disease or the necessary treatment for the pain.

Opioids

Natural

Opium

Morphine

Codeine

Semi Synthetic

Oxycodone

Heroin

Synthetic

Pethadine

Methadone

Fentanyl



Fig 10.2: Table of common opioids and a 200ml bottle of 10mg/ml 'Ordine' liquid morphine)

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It can often take days for the levels of morphine to become high enough to cause death. It is important for the doctor's legal safety that the process is slow. Indeed, it is the length of time taken that gives credibility to the argument that there was effort put into establishing 'just the right dose' of morphine.

If, for example, a single large dose of morphine was administered and death resulted, it would be almost impossible for the doctor to argue that their prime intention was the treatment of the patient's pain. Slow euthanasia is necessarily slow; it must be, to safely exploit this legal loophole.

Another way of understanding the process of slow euthanasia is to consider the link between cause and effect. The time taken for the morphine to end life muddies the water and blurs the connection between the cause (the commencement of morphine) and the effect (the patient's death). By blurring this link, a doctor can help a patient die and escape the legal consequences.

Slow euthanasia has a number of features that limit its appeal to a patient. Firstly, it is the doctor who is in control. While a patient might ask for this form of help, it will be the doctor who decides if and when it will be provided. Just because you - the patient - feel that now is the right time to begin the process, there is no guarantee that the doctor will agree.

The doctor may say that you should wait; wait until you become sicker, perhaps until your haemoglobin drops a few points, or your respiratory function tests deteriorate further. The sicker you are, the safer it is for the doctor to go down this path. If the doctor disagrees with you and thinks the 'best time' to help should be several weeks away, there is absolutely nothing you can do about it.

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Another drawback of slow euthanasia is the restriction on the range of drugs that a doctor might use to help a person die. The doctor's defense must be that they were treating the patient's pain (as opposed to causing death). This is why a pain-relieving drug like morphine must be used.

A doctor could not, for example, administer a large dose of a barbiturate. While a barbiturate might provide the most peaceful and quickest death, barbiturates are not pain-relieving drugs. A claim that a barbiturate was being used to treat pain makes no sense.

The use of morphine by doctors to end life has led to the common community misconception that the best drug to use to end a person's life is morphine - it must be. That's the drug that doctors use! This unfortunate misunderstanding leads to many failed suicide attempts.

‘Double M’ Therapy

For a person to die of a medically-administered morphine overdose, the process must be slow. Indeed, slow euthanasia can often take days or even weeks. Often the patient is given a sedative that keeps them asleep through the whole process; midazolam is the drug of choice.

Coupled with morphine, this morphine - midazolam mix (known as ‘Double M’ therapy) places the patient in an induced coma for the time needed to raise the morphine level sufficiently. Double M therapy allows the patient to sleep through their own death and gives rise to another name for the process - ‘pharmacological oblivion.’

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The doctor still makes the assessment about the need for larger and larger morphine doses. Here the decision is based upon a clinical assessment of the unconscious person, not on the patient's complaints about their pain.

In slow euthanasia, the doctor also chooses the place of death. It is unusual for slow euthanasia to take place in a patient's home. Usually it occurs in an institution, commonly a hospital or hospice.

In an institution, a team is often involved in providing care and several doctors might participate in the relentless increase of the morphine. This further blurs the link between cause and effect. This makes the process even safer for the medical staff involved. While slow euthanasia could take place at the patient's home, in practice this presents many logistical difficulties. The doctor would need to make many visits, perhaps several a day, to facilitate the relentless increase in drugs.

Also full nursing care is required; an unconscious patient needs to be moved regularly and watched constantly to ensure the flow of drugs is not interrupted. This is often an extremely difficult time for those close to the patient as they find themselves participating in this deliberate, slow death watch.

For these reasons, few people opt for slow euthanasia as their preferred choice for a peaceful, dignified death. More commonly, it is an option of desperation, when few alternatives exist. In such dire circumstances, if a doctor does offer to help (usually through a nod, a wink and an understanding), patients will grab the chance, reasoning correctly that this is better than nothing.

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Those who are left often see this as an example of a doctor helping someone to die. This leads to the commonly expressed view that there is no need for euthanasia legislation. People say ‘I can’t see what all the fuss is about with assisted suicide – it goes on all the time – doctors are always helping people to die.’

It is as well to remember that ‘what goes on all the time’ is the grim process of suspending a sick person by a thread between life and death for an arbitrary time, until the thread breaks.

That is slow euthanasia!

In Exit’s internal polling of over 1000 of our supporters, less than one percent (0.3%) of members said that they would prefer slow euthanasia compared to a Peaceful Pill (89%). Slow euthanasia is, therefore, one of the least-preferred methods of dying, and one that is usually avoided when other options exist.

Given a choice, people prefer to have control of the dying process. This is not the case with slow euthanasia. It is relatively rare to find someone who wants to spend their last days in a drug-induced coma. When people decide that their suffering is so great that death is preferable, they want their passing to be quick.

This is why slow euthanasia is almost always an option of last resort. It is the method accepted when nothing else is on offer, and the only alternative is relentless and ongoing suffering.

Another unfortunate consequence of slow euthanasia is the common belief that morphine is the best drug to end life. This reputation is undeserved and comes from the almost-universal use of morphine (or other opioids) in slow euthanasia, where doctors have little choice.

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While a single overdose of morphine may cause death, individual sensitivity and tolerance to these drugs make this an uncertain and unpredictable process. Morphine is best used to do the job it is designed to do, control strong pain. There are better euthanasia options available.

The Use of Heroin

Exit is occasionally asked about whether heroin can be obtained from ‘the street’ and used to end life. These questions are often prompted by media reports of people dying from a heroin overdose. In reality, there is little to be gained by using heroin.

As an opioid, heroin suffers from the same problems of tolerance and sensitivity discussed above. In addition, there is the question of the uncertainty of the dose with heroin. Because it has been acquired on the streets, one can never be exactly sure what or how much one has actually purchased. It also needs to be injected intravenously. In Exit’s experience, few elderly and seriously ill people have these skills.

Note: If heroin is taken orally, it turns back into morphine in the gut and offers no advantage over prescription tablet morphine, where at least the exact dose is known.

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The New Synthetics – Fentanyl and Carfentanil

The opioid fentanyl was first synthesized in 1960 by Belgium researcher, Paul Janssen. This drug and a number of structural analogues, including sufentanil, lofentanil and carfentanil were found to have a strong agonist effect on the opioid receptors in the brain and were immediately recognized as powerful analgesics. Fentanyl, the first to be marketed commercially as an analgesic is ~ 100x more potent than morphine, carfentanil, developed to sedate large animals, 10,000x more potent. In 1984, the Food and Drug Administration (FDA) declared all fentanyl analogues to be Schedule I substances (completely illegal and useless for medical purposes).



Fig 10.3 Schematic representation of the varying potency of different opioids

Fentanyl is a powerful fast-acting opioid prescribed for the control of strong pain. It is rapidly metabolised in the body by the (Cytochrome P450) liver enzyme and excreted. Indeed, this rapid breakdown of the drug means that the drug can sometimes be difficult to detect at post mortem. The oral ingestion of the drug results in lower plasma than that obtained by other available means of the drug's administration (transdermal, intravenous, buccal, or even as an aerosol (as used in 2002 in the Russian theatre hostage crisis, see: <http://rense.com/general31/opi.htm>

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Products that interfere with the enzymatic breakdown of the drug can significantly (and dangerously) increase blood levels of the drug. For example, the taking of grapefruit juice ‘may result in a potentially dangerous increase in fentanyl plasma concentrations. This can, in turn, increase or prolong adverse drug effects and may cause potentially fatal respiratory depression’. See: <http://www.empr.com/clinical-charts/pharmacological-effects-of-grapefruit-juice-with-medications/article/207375/>

Marketed forms of fentanyl include ampules for intravenous administration (eg a 10ml ampule containing 0.5 mg fentanyl) and skin patches with various delivery rates (eg 0.1mg in an hour).



Fig 10.4 Commercial ampoule of Fentanyl Citrate 0.5mg in 10ml

The analogue carfentanil is even more potent than fentanyl and is not marketed as a pharmaceutical product. It is only available illegally.

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Both fentanyl and the analogues have potential for use as end of life drugs. The narrow therapeutic index (the dosage range in which the drug is an effective analgesic) and the small quantities needed for lethal depression of respiratory function are important factors. A lethal dose of fentanyl is as little as 3mg when taken intravenously. However, larger quantities will be needed for reliable lethal oral administration unless metabolism slowing steps (eg the drinking of grapefruit juice) are adopted. For carfentanil, even smaller doses will end life.

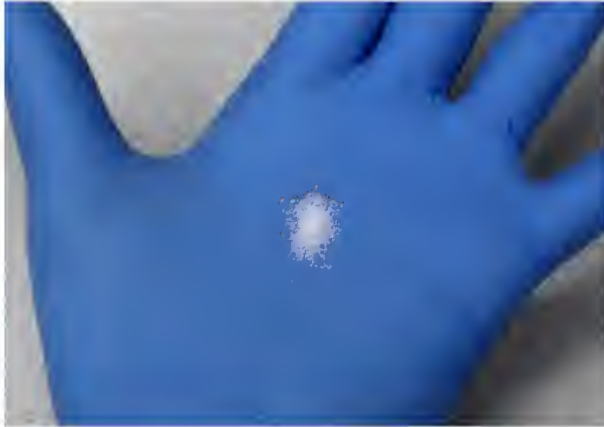


Fig 10.5 ~3mg of Fentanyl citrate powder

These drugs retain some of the sedative properties of morphine and the death from these drugs can be painless and quick. The rapid metabolism of these drugs may also give the possibility of undetectability regarding the cause of death.

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Difficulties in using fentanyl include the usual problems associated with all opioids of tolerance and sensitivity, although the (illegal) availability of the drugs in lethal amounts and the relatively small physical size of the lethal dose needed, reduces this problem. The availability of an effective antidote (naloxone) means that care should be taken to avoid interruption when taking fentanyl to die.

Legal Comment

Most prescription drugs (including fentanyl and morphine) can be lawfully possessed by a person if they have had it prescribed by a physician. Otherwise, the penalty for importing/possessing drugs such as fentanyl (<0.005gm) and morphine (<2 grams) in Australia, for example, is up to 10 years imprisonment and a \$360,000 fine. The higher the amount of the drug possessed, the higher the penalties. Similar penalties apply for Heroin that is an Australian 'border controlled drug'.

In the UK, heroin, fentanyl & morphine are all Class A drugs with potential maximum penalties of life imprisonment for the upper end of importation. In saying that, data shows that the penalties normally range from 3 years for the less serious offences (having a lesser role in the importation or importing small amounts).

In the United States heroin is a Schedule I Controlled substance. The penalties for importing <100gms are up to 20 years imprisonment and a fine up to one million dollars. Penalties for the importation of >100gms range up to life imprisonment and fines of up to ten million dollars. Fentanyl and morphine in the US are Schedule II Controlled Substances and share the same penalties as Schedule I drugs listed above for lesser amounts. Larger amounts can mean life imprisonment.

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Conclusion

One final point on the opioids. If one does die taking these drugs, the death is likely to be very peaceful. Morphia is, after all, the goddess of dreams!

To recap, the problems common to all opioids include tolerance, sensitivity and the existence of an effective and fast-acting antidote. These issues make the use of the commonest opioids (eg morphine, heroin and methadone) less desirable than they may first appear. The purity of illegal heroin is also an issue of concern. The growing availability of the potent synthetics provides some new and effective options. Although, again, the question of purity of illegal fentanyl analogues is a problem.

The Exit RP Test for Opioids

The opioids range widely on the RP Test. When used as a drug and taken as a single dose by a person wanting to die, the difficulty of establishing the lethal dose of the slower opioids significantly reduces Reliability (Morphine 4/10, Fentanyl 8/10). Peacefulness, however, is very good (9-10/10).

Minor criteria scores are varied. Availability (3/5), sometimes morphine or fentanyl is readily available – eg if a person is suffering from a recognised painful disease. But the use of the opiates as drugs of addiction, and their place in the illegal narcotic trade, can also make them very difficult to obtain. Purity is always an issue with the illegal street opioids. Preparation is easy (5/5), although constricted ‘pinpoint’ pupils will often alert a medical officer to the presence of the slower opioids in the system (Undetectability = 2/5, 4/5 for Fentanyl).

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Death from morphine can also take some time, depending on one's tolerance, and resuscitation. Frustration and failure can occur if someone intervenes and if the opiate antagonist naloxone is used (Speed = 2/5). There are no safety issues (Safety = 5/5). The drugs have a moderate shelf life (Storage = 3/5).

Exit RP Test - Opioids

Criteria	Score (Morphine)	Score (Fentanyl)
Reliability	4/10	8/10
Peacefulness	10/10	9/10
Availability	2/5	3/5
Preparation	5/5	5/5
Undetectability	2/5	4/5
Speed	2/5	3/5
Safety	5/5	5/5
Storage	3/5	3/5
Total	33 (66%)	40 (80%)